EP0652002

Publication Title:

Methods for inhibiting cartilage degradation

Abstract:

A method of inhibiting cartilage degradation comprising administering to a human or other mammal in need of treatment an effective amount of a compound having the formula <CHEM> wherein R<1> and R<3> are independently hydrogen, -CH3, <CHEM> or <CHEM> wherein Ar is optionally substituted phenyl; R<2> is selected from the group consisting of pyrrolidino and piperidino, a pharmaceutically acceptable salt or solvate thereof.

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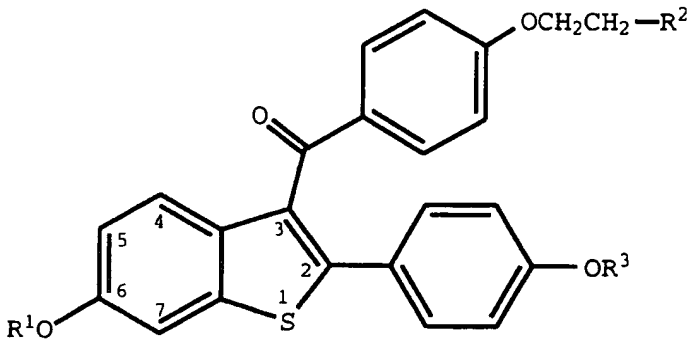
(71) Applicant : **ELI LILLY AND COMPANY**
Lilly Corporate Center
Indianapolis Indiana 46285 (US)

(72) Inventor : **Williams, Daniel Charles**
12163 Chateau Court
Fishers, Indiana 46038 (US)

(74) Representative : **Tapping, Kenneth George et al**
Lilly Industries Limited
European Patent Operations
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

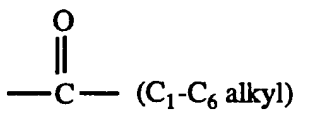
(54) Methods for inhibiting cartilage degradation.

(57) A method of inhibiting cartilage degradation comprising administering to a human or other mammal in need of treatment an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



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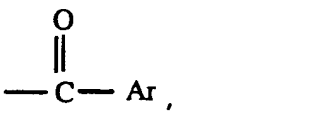

wherein Ar is optionally substituted phenyl ;

R^2 is selected from the group consisting of pyrrolidino and piperidino, a pharmaceutically acceptable salt or solvate thereof.

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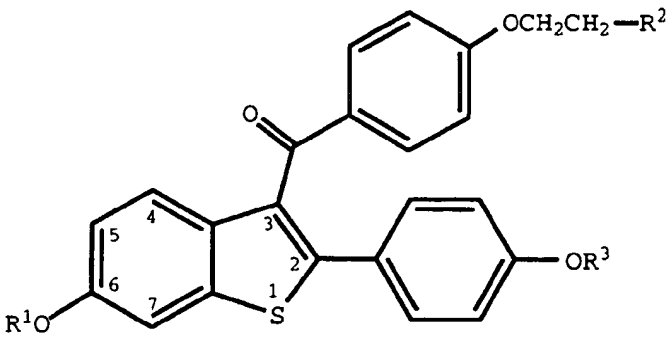
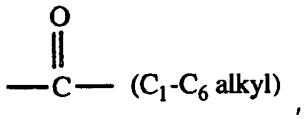
Cartilage is a proteinaceous material found in the joints of mammals. It is an elastic, spongy substance which covers the articular surfaces of the bones within the synovial cavity. The presence of cartilage, with its special properties of compressibility elasticity and deformability, permits joints to carry out there two major functions which are to bare weight and to facilitate locomotion.

Degradation of joints occurs in various diseases including rheumitoid arthritis, psoriatic arthritis, osteoarthosis, hypertropic arthritis, and osteoarthritis. Further, acute inflammation of joints may be accompanied by destruction of the cartilage. Examples of diseases involving acute joint inflammation are yersinia arthritis, pyrophosphate arthritis, gout arthritis, and septic arthritis. Also, another factor that may be conducive to destruction or degeneration of cartilage is treatment with cortisone

This invention provides methods for inhibiting cartilage degradation in a human or other mammmal, comprising administering to a human or other mammal in need of treatment an effective amount of a compound of formula I



wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



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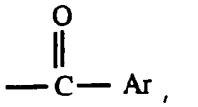


wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-aroylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting cartilage degradation. The methods of treatment provided by this invention are practiced by administering to a human in need of inhibition of cartilage degradation a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit cartilage degradation. The term inhibit is defined to include its generally accepted meaning which includes phrophylactically treating a human subject to incurring cartilage degradation, and holding in check and/or treating existing cartilage degradation. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated

as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent No. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Substituted phenyl includes phenyl substituted once or twice with C_1-C_6 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methane-sulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferable salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as aliphatic and aromatic amines, aliphatic diamines and hydroxy alkylamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylene diamine, cyclohexylamine and ethanolamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as agaragar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit cartilage degradation, according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed

to effectively inhibit cartilage degradation.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route to an aging human (e.g. a post-menopausal female). For such purposes the following oral dosage forms are available.

Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of the compound of formula 1 wherein R^2 is piperidino, (raloxifene), that have been made include those shown below:

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.
A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.
Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thor-

oughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

Formulation 8: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

ASSAY #1

Rabbit articular chondrocytes are placed in culture. Various concentrations of the compound of the invention (10^{-9}M to 10^{-5}M) and Sodium ^{35}[S]ulfate are added to the culture simultaneously in serum-free medium. After 48 hours, the amount of radiolabel incorporated into the cell and matrix (extracted with 4M guanidinium chloride) is evaluated and compared against control cells, to determine effect of compounds on proteoglycan synthesis.

ASSAY #2

Rabbit articular chondrocytes are treated with various concentrations of the compounds of the invention (10^{-5}M to 10^{-9}M) in the presence and absence of a constant concentration of estrogen (10^{-8}M), and proteoglycan synthesis is evaluated as described above.

ASSAY #3

Rabbit chondrocytes are isolated and radiolabled as in Assay 1 above. The cells are then treated with interleukin-1β (10 ng/mL) for 24-72 hours both with and without a compound of the invention. The loss of proteoglycan in each of the cell cultures is observed. Active compounds will block the loss of proteoglycan.

ASSAY #4

Bovine cartilage is cut into 5 by 1 mm slices and labeled with sodium ^{35}[S]ulfate for 48 hours and then treated as in Assay 3. Active compounds are expected to block the loss of proteoglycan from cartilage.

ASSAY #5

In order to evaluate whether the compounds of the invention induce TGF-βs(1, 2, 3), rabbit chondrocytes are treated for 24-72 hours with various concentrations of compounds of the invention and the conditioned media is assayed for the presence of latent and active TGF-βs.

ASSAY #6

Rabbit chondrocytes are treated with interleukin-1β (10 ng/ml) for 48 h in serum-free medium in the presence and absence of a comound of the invention. At the end of the incubation period, the medium is removed and assayed for neutral protease activity, using ^{3}[H]-casein as sustrate for the enzyme activity. An active comound inhibits the production and/or activity of the enzyme induced by interleukin-1.

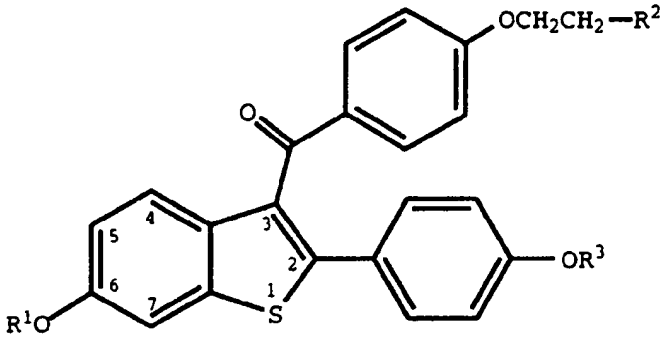
ASSAY #7

$C_{57}B1$ mice receive intermittent subcutaneous injections with a compound of the invention beginning at one to six months of age. The course of treatment continues for 6-12 months. The animals are sacrificed at 18-20 months of age and their knee joints are evaluated for evidence of osteoarthritis. Decreased incidence or severity of osteoarthritis damage is indication of the efficacy of treatment.

Activity in any of the above assays indicates that compounds in the invention are useful in the inhibition of cartilage degradation.

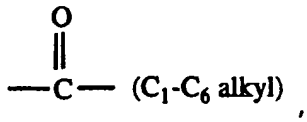
Claims

1. The use of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



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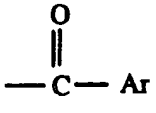


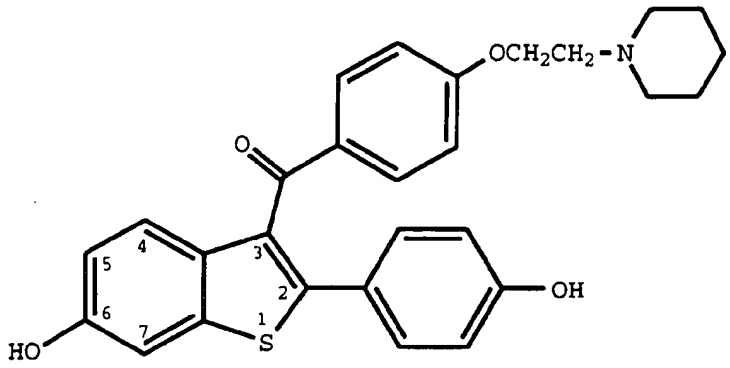
wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting cartilage degradation.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.

3. The use of Claim 1 wherein said medicament is prophylactic.

4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 7525

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	US-A-5 075 321 (SCHREIBER) 24 December 1991 * column 2, line 47 - line 54; claims 1,13,28 *	1-4	A61K31/445 A61K31/40 A61K31/38
A	DATABASE FILE 187, FDC REPORTS Dialog Information Services 1987-1993, Accession No. 00089403, *on-line abstract* & THE PINK SHEET, vol. 55, no.16, 19 April 1993 'Lilly's raloxifene entering phase III for osteoporosis'	1-4	
D,A	US-A-4 418 068 (JONES CHARLES D) 29 November 1983 * the whole document *	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	23 February 1995	Foerster, W

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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